Docket No.: ALXN-P02-089
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Figdor et al.

Application No.: 10/625,202 Confirmation No.: 1242

Filed: July 23, 2003 Art Unit: 1648

For: COMPOSITION AND METHOD FOR MODULATING DENDRITIC CELL-T CELL INTERACTION Examiner: M. G. Hill

REMARKS ACCOMPANYING PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Final Office Action dated October 6, 2009 and the Advisory Action dated January 5, 2010, Applicants hereby request a Pre-Appeal Brief Review. A request for a one-month extension of time and appropriate fee are submitted concurrently herewith. Please consider the remarks below which accompany Request form PTO/SB/33, filed herewith.

Claims 1, 3, 4, 6, 7, 19, and 23-27 are rejected under 35 U.S.C. § 112, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse. First, the Examiner asserts that the currently claimed invention can both increase and decrease the immune response and the difference in immune response in the methods is not differentiated by distinct method steps. See, Office Action, page 3, lines 12-16. Applicants disagree for the reasons of record. See, Office Action Response of December 4, 2009, pages 2-3. In particular, while the specification teaches that certain embodiments of the application relate to methods of increasing an immune response in an animal, the immune response in that context is against a specific antigen. Briefly, an antibody may be attached to a specific antigen and this antibody-antigen conjugate may be used for targeting the

antigen to dendritic cells, and subsequently inducing an immune response against the specific antigen (e.g., page 15, lines 3-26 and the paragraph bridging pages 15 and 16).

By contrast, the claimed invention (e.g., claim 1) is directed to a method for reducing a T-cell mediated immune response in an animal by using a naked antibody that binds to the DC-SIGN on the surface of a dendritic cell and blocks the interaction of the dendritic cell with a T cell. Such method results in an inhibition of T-cell mediated immune activity. Contrary to the Examiner's assertion, one of skill in the art could readily differentiate these two inventions, which require different forms of an antibody (the first requires an antibody-antigen conjugate, whereas the second uses a naked antibody) and cause different outcomes (the first causes an increase in a specific immune response, whereas the second causes a decrease in immune activity). Hence, the two inventions do have distinct method steps.

The Examiner further asserts that MPEP § 2164.02, quoted by Applicants in reference to the acceptability of *in vitro* examples, refers to small pharmaceutical molecules not antibodies. Applicants disagree for the reasons of record. See, Office Action Response of December 4, 2009, pages 3-4. In fact, the quoted section of the MPEP itself is not directed to small molecules. Even if the particular case law being cited (*Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985)) involves a small molecule, the MPEP makes no distinction between a small molecule or a large molecule. In addition, Applicants submit that the distinction drawn by the Examiner between a small molecule and a large molecule (e.g., an antibody) is irrelevant to the enablement rejection. The specification also demonstrates that the disclosed antibodies bind to the DC-SIGN, and inhibit the interaction between the DC-SIGN on the surface of dendritic cells and an ICAM receptor on the surface of T cells. The Examiner did not explain why the type of molecule, e.g., an antibody as compared to a small molecule, would make any difference in evaluating enablement.

Further, the Examiner states that the claimed method requires binding to a cell and then triggering further action in the form of a reduced immune response and that the examples and the prior art do not show this function. See, Office Action, the paragraph bridging pages 3 and 4. Applicants disagree for the reasons of record. See, Office Action Response of December 4, 2009, page 4. Applicants point out that the Examiner has incorrectly characterized the claimed method by

stating that "the method requires binding to a cell and then *triggering further action* in the form of a reduced immune response" (Office Action, page 3, last line, emphasis added). In the claimed method, an anti-DC-SIGN antibody binds to its target (DC-SIGN represented by SEQ ID NO: 2), thereby blocking the DC-SIGN from further interactions with a T-cell. With DC-SIGN blocked, the further actions (e.g., interaction with a T-cell) that are required for an immune response cannot occur, resulting in a decreased immune response. Thus, the binding of the antibody does not trigger further action as the Examiner asserts; to the contrary, it blocks further action. Accordingly, in the claimed method, an antibody may actually be better than a small molecule since the antibody may block an interaction between DC-SIGN and a T-cell more efficiently due to steric interference. All that is required is for the antibody to bind to DC-SIGN and thereby block interaction of DC-SIGN with T-cells.

Applicants reiterate that *in vivo* efficacy data are not required to enable an *in vivo* use and that *in vitro* test results are generally predictive of *in vivo* testing results. See MPEP § 2164.02; also see *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985). Scientifically sound explanations, backed by *in vitro* testing, are widely accepted as sufficient evidence to support claims drawn to subject matter commensurate in scope with that support. See *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). The instant application provides several examples, including *in vitro* data derived from cell based assays, to support the claimed subject matter. For example, Example 2 demonstrates that an antibody against DC-SIGN can inhibit the interaction between DC-SIGN (on the surface of the dendritic cells) and an ICAM receptor (on the surface of the T cells). See, e.g., paragraph [0100] and Figures 2A and 2C. Example 6 further demonstrates that: (1) anti-DC-SIGN antibodies prevented the clustering of dendritic cells with ICAM-3-expressing K562 cells (Figure 6B); (2) anti-DC-SIGN antibodies inhibited the clustering of dendritic cells with PBLs (which include T-cells) (Figure 6C); and (3) most importantly, anti-DC-SIGN antibodies inhibited the activation of T-cells when T-cells were mixed with dendritic cells (Figure 6D), as discussed in Example 6 and Example 7. These assays are representative of what occurs *in vivo*, i.e., there are interactions between DC-SIGN and T cells which initiate an immune response (see, e.g., paragraph [0093] of the instant application). The application also teaches and enables reducing an immune response by inhibiting an interaction between DC-SIGN and a T cell. Therefore, the application teaches and enables the

method as recited in independent claim 1. A person of ordinary skill in the art can make and use the claimed methods based on the *in vitro* data and other teachings of the specification, without undue experimentation.

In addition, Applicants emphasize that various publications have demonstrated that the *in vitro* evidence provided in the specification is representative of what occurs *in vivo*. See e.g. Ingulli et al., J. Exp. Med., vol 185, 2133-2141 (1997), Janeway et al. (2001), Immunobiology, 5th edition, pages 20-21, and Pereira et al., J. Immunother. 30:705-714 (2007) (previously submitted and discussed in the Office Action Response of June 8, 2009, pages 9-10). In particular, it is reported that an anti-DC-SIGN antibody, when administered *in vivo* in a nonhuman primate model, successfully bound to DC-SIGN expressed on the surface of dendritic cells *in vivo*. See Pereira et al. In view of the examples provided by the specification and the additional evidence as previously submitted by Applicants, one of skill in the art would recognize that an anti-DC-SIGN antibody can successfully bind to DC-SIGN *in vivo* and block interaction between DC-SIGN and a T-cell *in vivo*, thereby resulting in a decreased immune response *in vivo*.

Further, Applicants submit that the Examiner has the burden to provide reasons for a conclusion of a lack of correlation with *in vitro* testing or an *in vivo* animal model (see MPEP 2164.02). In this case, the Examiner has merely asserted that the level of unpredictability in the art is high and on this basis concludes that one skilled in the art would not associate *in vitro* efficacy with *in vivo* treatment. The Examiner has not provided any specific reasons to doubt that the *in vitro* data correlate with *in vivo* efficacy. The Examiner has not provided any evidence to suggest that the instantly claimed methods would not be operative with respect to reducing T-cell mediated immune response *in vivo*, thereby failing to meet the burden of establishing a *prima facie* case of lack of enablement.

Finally, the Examiner asserts that the specification does not teach the amount or type of reduced immune response, the significance *in vivo* or what that level of reduction produces (see, Advisory Action page 2). Applicants disagree. Applicants assert that the specification does teach the amount and type of reduced immune response, the significance *in vivo* and what that level of reduction produces. See, for example, specification paragraphs [0032] through [0035].

Specifically, the specification teaches that anti-DC-SIGN antibodies bind to DC-SIGN, and inhibit the interaction between the DC-SIGN on the surface of dendritic cells and an ICAM receptor on the surface of T cells. The specification teaches that such interactions include the adhesion of T-cells to dendritic cells, for instance in dendritic cell-T-cell clustering and T-cell activation. These dendritic cell-T-cell interactions are involved in generating an immune response, such as primary sensitization/activation of T-lymphocytes, and co-stimulation of T cells; as well as processes such as chemical signaling, endocytosis and transepithelial transport. As disclosed in the specification, specific applications include, for example, preventing or inhibiting immune responses to specific antigens and immunosuppression, for instance to prevent transplant rejection. Therefore, one of skill in the art would have understood the significance of the invention *in vivo* and what to expect from the *in vitro* examples.

In sum, Applicants submit that the pending claims are enabled throughout their scope. Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

CONCLUSION

In view of the above remarks, Applicants believe the pending application is in condition for allowance. Early and favorable consideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants believe no further fee is due with this response. However, if a fee is due, please charge our Deposit Account No. **18-1945**, under Order No. **ALXN-P02-089** from which the undersigned is authorized to draw.

Dated: February 4, 2010

Respectfully submitted,

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